THE ABUNDANT PROMISE OF ULTRASOUND IN NEUROSURGERY

A Broad Overview and Thoughts on Ethical Paths to Realizing Its Benefits

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"Shipwrecked we just float, O favorable wind arise,
May we one more time gaze upon that familiar trait."

"For years my heart was in search of the Grail
What was inside me, it searched for, on the trail."

– Hafiz

Dedication

Amir Manbachi would like to dedicate this book

To the women in our lives, and in support of the feminism movements around the world!

Especially for:

"*Woman, Life, Freedom*"
(Femme, Vie, Liberté)
(آزادی زندگی زن)

May we keep learning from our failures as a society:

From the story of Mahsa Amini, the young Persian woman who lost her life because she showed an inch of hair in 2022; or the woman who had to flee her birth country in fear, without her husband's legal *travel permission* amidst the pandemic lockdowns, just to save her life from domestic abuse and non-supportive, anti-feministic laws.

Here's to all the men, women, and others who stand up for a more fair, inclusive, and empowering society for all of us!

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First Exposures to Neurological Disorders

> "*Proud of you and everything you have accomplished! I'm sure between your education ingenuity and your artistic music talents, you and agha Reza*[*] *will have a great life ahead of you! If we don't see each other again, I want you to—*"

I interrupted my uncle halfway through his sentence, even though interrupting an elder was a major no-no in the Persian culture. But I had no choice. I was afraid to hear the rest of what he had to say!

To the best of my memory, these were the last words spoken to me by my uncle, as our family departed Iran to embark on our immigration journey to Canada. My uncle's name was *Mansoor* (meaning "victorious" in Farsi). He had gone through a lot and was a man of great integrity. Uncle Mansoor had lost his father at a young age and had managed to support himself, his mother, and his siblings through craftsmanship during his childhood. After suffering a work-related eye injury, he would eventually find his way to working in healthcare in Iran. Given my age, I couldn't comprehend the depth of the traumas he had experienced. Despite myriad obstacles, Uncle Mansoor single-handedly supported his elderly mother, my grandmother, through her final moments—with no governmental assistance or support from the rest of the family. If he had a middle name, it should have been *Righteousness.* He lived a simple life, full of love. He had a heart of gold and was sincere, pure, and down to earth.

My brother and I have many cherished memories of Uncle Mansoor. I remember his retirement when I was around 10 years old—as he had more free time, he visited our family often. Uncle Mansoor used to take us to hike the

[*]The word "agha" means "Mr." in Farsi. "Reza" is my older brother's name; it means "content," and that is exactly how I would describe him: wise, calm, and content.

beautiful mountains around Iran, to some of the unique natural hot springs, and even to ritual festivities, such as Ashoora. We used to get together to watch the impeachment of politicians on TV and take road trips on the back of our family truck. As we made our descent from our mountain hikes, he would often stop to buy us authentic local food from the people and vendors making their livings in the mountains. Even now, the aroma of lentil soup or the sight of fresh sunny-side-up eggs instantly takes me back to memories of hiking with him. Despite the age gap, we never ran out of things to talk about.

When Uncle Mansoor said those last words to me, I don't know exactly what he was thinking. But because he referred to my relationship with my brother, my suspicion tells me that he may have thought of his own younger brother, Mohsen, who had died at a young age due to glioblastoma multiforme, a fatal brain tumor. Despite multiple surgeries performed in rapid succession, Uncle Mohsen did not survive to see his children—my cousins—grow up. Given this context, it made sense for my mind to go to the extreme when Uncle Mansour said those words to me at a farewell moment. Later, I learned that the last few years of his life, Uncle Mansoor also suffered from a combination of neurological disorders. Sadly, I was not there for him during these struggles—and this pains me, given how he was always there for everyone around him. Although I did not witness the symptoms, I was told that shortly after my grandmother passed away, his health also deteriorated drastically. He had difficulty walking with a weakened leg, and he was tired of constantly shaking and feeling hot. He had Parkinson disease, but it seems that there may have been other factors in play, such as dementia. Long story short, I did not get a chance to see him again. Losing two uncles to neurological disorders has left a mark on me.

My reaction at the time was that if I could not help the former generation that was instrumental to my upbringing, perhaps I could try to help the next generation. I realize how grand a dream this is, and no one person can help change the entire course of an entire field. But I knew I could do something. I knew I could take things just one step further, and I was determined to do so.

Thirteen years later, history repeated itself: I was moving from Canada to the US for my postdoctoral fellowship at Harvard Medical School, and an aunt made me feel home in Massachusetts. Her name was Mansooreh (literally meaning "female victorious"), also known as Aunt Mary. Aunt Mary's doors and arms were always open to me, and soon it became expected that I would visit her in Framingham, Massachusetts, every weekend. The commute was only an hour by train, and I loved train rides because I could get work done on my laptop. Aunt Mary was known for her cooking. In fact, she used to cook so much food for me that most of my lab mates knew about her, her hospitality, and her cooking without having even met her—she made so much food that I had to take the food to the lab and share it with my colleagues! Her homemade fresh hummus was her signature.

Professional advancement is a double-edged sword: it allows for all types of growth and development, but often requires personal sacrifice. Within a year of my arrival in Boston, I was invited to join the faculty at Johns Hopkins University in Baltimore. As thrilling as this was, I couldn't help but feel sad that it would take me farther away from Aunt Mary. Realizing that she did not have that many friends or family, and given the strong bond we had formed, I promised her that I would go back to visit her as frequently as I could. The city of Baltimore did not have the best reputation, at least from the outside world, and I would take any opportunity I could to take the Amtrak train to visit her. Boston was a happy middle for both my parents driving from Toronto, and for me taking the night train. For the next few years, getting together at Aunt Mary's house for the American holiday of Thanksgiving and for the Persian New Year's Eve (March equinox) became a ritual.

March 2019 was the last time this lovely group got together. An emergency at work made me rush back to Baltimore, cutting a trip to Aunt Mary's house short. I promised her that I would return soon. She complained to me about her chronic pain and her arthritis and had asked me if I could help her find a "real" solution for her pain the next time I visited. I told her that I would absolutely help, fully realizing that not much progress had (or still has) been made in pain management research. Upon my return to Baltimore, I suffered an injury that made traveling quite inconvenient. Six months later, my mother and I were planning a trip to visit Aunt Mary when I saw her son's post on Facebook about her passing.

Aunt Mary's passing reminded me of the path I had wanted to walk. Painfully, it also reminded me that I had not done anything real about it. After all, I had barely even started my career and had no real resources to be able to take any steps forward. But one thing seemed certain—I sensed that all my uncles and aunts were trying to inspire me to tackle unsolved neurological disorders, from pain, to Parkinson disease, to dementia, to brain cancer! Every day, I think about how these individuals influenced my life, and how the previous generation of my beautiful extended family helped me grow and settle in different countries amid difficult times of revolution, war, sanctions, and immigration. However, when they passed, I had neither the time nor the money to be able to help them as much as I would have liked (typical lifestyle in America these days!). Not much has changed with respect to time and money for me, but I like to think at least now I have the research resources to be able to take at least one step toward scientific studies in these fields. I am hopeful that at last, I may make an impact.

First Exposures to the World of Sound

My first exposure to the world of sound was when I was 4 years old. My brother Reza was 8, and our family was still living in Iran. From the time Reza and I were very young, my parents put in a heroic effort with respect to

our education and extracurricular activities, such as learning world music and other languages. Perhaps it was this early exposure to both music and languages that made us audial learners. Because I was too young to even hold a musical instrument, my dad hired a private tutor to teach Reza how to play a musical instrument called a "tar." *Tar* means "string," and by some accounts, this instrument is the basis for the guitar. When Reza first started taking lessons, my dad joined in so that he could learn, too. As a 4-year-old, I felt excluded and rebelled, making noises and generally being a disturbance. My mom had to take me out of the house and distract me so that my brother and dad could comfortably learn from this private tutor. Despite my mom's efforts, I somehow managed to disrupt the sessions anyway. I remember one instance in particular, when I was behind the door trying to understand what it was that Reza and my dad were learning that I couldn't. As I leaned into the door to listen, it opened—announcing my presence to the instructor, my dad, and my brother. The instructor smiled softly, looked at my dad, and said: "He wants to learn something too!"

Dad's opinion, primarily influenced by the culture of the Middle East at the time, was that if you take care of the older son, the other children will follow the path and will in turn learn from the eldest. However, I never understood this concept and reasoned that it was likely a way for my father to save money. It was demotivating, especially because I liked rhythms and beats and percussion instruments more than melody. As a child, I liked to pretend to drum on the lid of plastic jars used to sell dairy products in Iran.

One day, the music tutor brought along a Persian drum called a "tombak." The instrument looks like a goblet-shaped wooden drum with a goat skin stretched over the top. It is placed on the drummer's lap and played with the snap of the fingers. I was mesmerized by its sound. Four years later, when I was 8, our family attended an orchestra concert led by the famous Hossein Dehlavi. This was the very first concert I attended, and I hold dear a very fond memory from the experience. An older guru named Ostad (guru) Mohammad Esmaeili oversaw the percussion instruments of the orchestra. On the stage, he had a whole army of tombak players following his lead in a percussive ensemble. For one portion of the concert, all of the melodic instruments of the orchestra stopped playing and gave up the stage to the percussion players. The percussionists' ability to create music with no melody was mesmerizing; it was like magic. The back-and-forth and the duets among the percussion players just felt like a rhythmic dance. This experience made me realize that I just had to play that instrument—and so I did.

Learning music, especially world music, is one of the best skills I have enjoyed being exposed to. It has opened my eyes to the world of sound and acoustics. Since I picked up a tombak at that age, not a day has gone by without me listening to or playing music. I have had the opportunity to interact with some world-renowned gurus of Persian traditional music over

the years, and this has played a part in shaping my personality and my mission in life. Getting to meet, learn from, and work with icons such as MohammadReza Shajarian, Hossein Alizadeh, MohammadReza Lotfi, Kayhan Kalhor, Pejman Haddadi, Hossein Behrouzinia, Arzhang Kamkar, Arash Farhangfar, and Homayoun Shajarian changed my outlook on life, even as a scientist. Such interactions will forever remain on my gratitude list.

First Exposures to the World of Ultrasound

Lessons in Radiology from a Physical Therapist, a Dentist, and the Teenage Mutant Ninja Turtles™

As Reza and I grew up in the Middle East, everything "American" was cool. But because our governments didn't have a friendly relationship, few American toys and games made their way into our country. An exception to this was the Teenage Mutant Ninja Turtles™ cartoons of the 1990s! You might be wondering what link exists between the Teenage Mutant Ninja Turtles™ and ultrasound... Allow me to elaborate.

After becoming obsessed with the Ninja Turtles TV show, Reza and I started impersonating the Ninja Turtles during our regular games. The problem was that my brother was four years older than me, and probably twice my height at the time—this made it an unfair battle! I had no choice but to look for creative ways to defend myself. One day as we played, I took the role of Donatello, whose weapon was a bō staff—a long, wooden stick. Reza surprisingly elected to play Michelangelo, whose weapon was the nunchaku—which have a much shorter reach. In the midst of the battle, Reza lunged at me, and I instinctively rammed my staff forward, making direct contact with poor Reza's groin. I expect that this hurt Reza as much as it sounds like it did. He complained all night and the next day, and our parents ultimately had to take him to see a radiologist, who would use magic "sound imaging" to assess the damage. (To those concerned, Reza was fine and is now a father of two beautiful, lovely, and smart children.)

A non-turtle instance when I heard the word "ultrasound" was when my dad needed to see a physical therapist for his back pain. Dr. Hashemi was a patient man who did not mind dealing with annoying and curious children like me. I remember him trying to explain to me how the physical therapy worked. He said, "This thing here is a music toolbox; we just don't hear the notes. The notes convert to heat and heal the back!" In hindsight, I appreciate how much of an effort he put into explaining things to me clearly and simplistically—even though I could not comprehend the concept at the time.

Another memorable character from my childhood was our family dentist, Dr. Darabi. His clinic was just upstairs from my uncle's spine surgery clinic, and this proximity fostered a good relationship with our whole family. Dr. Darabi was a lovely, charming, welcoming clinician. Since I liked to touch

his instruments and he liked talking, we had a natural rapport, and he would explain different pieces of his dental equipment to me. I remember hearing from him as a child about how dental cleaning can be done using a sound actuator, which I now understand to be another application of ultrasound. The field had so much to offer, but it was far too early for me to connect the dots.

"You can only connect the dots looking backwards."

Despite these early encounters with ultrasound, it was not until I began my graduate studies at the University of Toronto that I fell in love with ultrasound as a field and began to appreciate the limitless applications of acoustics for patient care. This was all thanks to my Ph.D. advisor, Professor Richard S.C. Cobbold. Even as a retired professor, he retained tremendous enthusiasm for his role. We remain in touch a decade later and were able to virtually celebrate his 90th birthday this past December.

I learned so much from Professor Cobbold. He never showed stress and treated everyone with respect—even though he could easily grill you scientifically if he wanted to. He was a professional, respectful, and encouraging mentor who we learned from him on a daily basis. He knew how to give feedback and criticize your work without criticizing you as a person, which is frankly a rare trait in the world of science and academia. He had published *The Foundations of Biomedical Ultrasound*, a bible in the field of ultrasound. Each time I reread it, even after a decade, I learn something new. Professor Cobbold backed me up in several instances, particularly when I came up with my first invention disclosure. He taught me how to think ethically in terms of the inventorship. He also helped me launch Spinesonics, my very first company. The company didn't last, but the lessons did. Although Professor Cobbold was my Ph.D. advisor, none of these things were part of his job description. He selflessly supported me in any way he could.

Focusing on the Here and Now

At Hopkins, I am grateful to so many individuals who have helped me find myself and reinvent my identity as an academic and an innovator in the fields of ultrasound and neurosurgery. I am particularly grateful to Dr. Nicholas Theodore, Betty Tyler, Dr. Youseph Yazdi, Dr. Alfred Emondi, and others for walking with me during the ups and downs of my career path.

This book is an introductory remark to the world of ultrasound and primarily exists because Dr. Kert Edward from SPIE Press invited me to write it after I published a shorter audiobook version for lay audiences last year: *Handbook for Clinical Ultrasound: Beginner's Guide to Fundamental Physics & Medical Ultrasound Applications*.

Although Dr. Edwards tasked me directly with bringing this book to life, after careful consideration and debate, I decided that a more meaningful product would involve my fellow lab members as co-authors and contributors.

As you read the various chapters of this book, it will become obvious to you that some chapters are either written by (or influenced by) clinicians, while others are written by (or influenced by) engineers, fabrication experts, physicists, ethicists, or patient advocates. We have deliberately left it that way because these various backgrounds produce intriguing perspectives for diverse audiences. This diversity represents the field of ultrasound well, as it is by nature a multidisciplinary tool that has use in radiology, biomedical engineering, mechanical engineering, electrical engineering, physics, and more.

Among the many co-authors of these chapters ahead, I would like to especially thank Kelley Kempksi Leadingham and Dr. Eli Curry, two of our research scientists on the HEPIUS Innovation lab's team. These two scholars took a much more hands-on approach to writing and became co-editors of this book as a result.

Looking Forward to the Great Unknown

Not being able to help Uncle Mansoor or Aunt Mary was discouraging and depressing—but was also humbling and motivating. When I look at my career, I see that I have been given a chance to work at one of the best healthcare institutions in the world. I am also lucky to have been awarded a contract from the Department of Defense, alongside Nick Theodore, to be able to address some of the promises of ultrasound for patients with spinal cord injury. It is the acknowledgement of these blessings that motivates me every day to get up, make the commute to work, and do my best, in the hopes of making an impact in the field. It is the ambitious nature of the vision and the hunger to do more that keeps me going.

Although I regret that I could not help the previous generation, I hope to one day look back and see that I took even just one step toward giving future generations something that we did not have. This book is an attempt toward that goal! I hope it will serve as a meaningful step toward raising awareness and education about the limitless promises of ultrasound, especially in the field of neurosurgery.

Despite all the challenges, I have no doubt that the future is bright for this field. I am particularly encouraged by the advances of the noninvasive therapeutic ultrasound treatments and how incision-free brain surgery is starting to become a reality. These advances are largely influenced by the Focused Ultrasound Foundation in Charlottesville, Virginia—a group of brilliant and warm, collaborative colleagues focused on faster, smoother, and easier transition of these treatments.

Because of all these efforts, I have no doubt that the future is bright. I see the keen intelligence of my 6-year-old niece, Nava, when she asks me dozens of questions on all sorts of topics. I see it when I look at the eyes of my 6-month-old nephew, Nima, who peers at me somberly when I try to introduce him to a music instrument like the tombak. This generation will

have more and will be able to do more than we did. It is my fervent hope that projects like this book will take us one step farther in terms of leaving the world better than we found it. I believe in the power of sound, ultrasound, and acoustics—especially in a field of much necessity, such as neurosurgery. If this book helps you to think the same way, or if you already do, please join me to partner up and aim to make an impact in this field.

Amir Manbachi, Ph.D. is a Persian-Canadian Ultrasound Engineer and Biomedical Engineer from Toronto. He is an Assistant Professor of Neurosurgery, Biomedical Engineering, Mechanical Engineering, Electrical and Computer Engineering at Johns Hopkins University, focusing on studying the fundamentals and novel clinical applications of ultrasound. He is the engineering co-PI on a $13.48M award from Department of Defense and is responsible for the assembly of a world-class team of pioneers, including 60 individuals from clinical, academic, and industry settings. He is the co-Director and founder of the HEPIUS Innovation Labs, focusing on the next generation of wearables and implantable medical ultrasound devices for spinal cord injury patients: HopkinsMedicine.org/Neuro/HEPIUS